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EXAMINER

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ART UNIT PAPER NUMBER

1644

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Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center">Office Action Summary</p>	<p>Application No.</p> <p align="center">09/761,636</p>	<p>Applicant(s)</p> <p align="center">ACHEN ET AL.</p>	
	<p>Examiner</p> <p align="center">" Neon" Phuong Huynh</p>	<p>Art Unit</p> <p align="center">1644</p>	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 1/2/03; 1/10/03.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 12-18, 23-26, 49-63 and 72-103 is/are pending in the application.
- 4a) Of the above claim(s) 4, 14-17, 25, 52, 56-62 and 89-103 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 12, 13, 18, 23, 24, 26, 49-51, 53-55, 63 and 72-88 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-4, 12-18, 23-26, 49-63 and 72-103 are pending.
2. Newly submitted claims 88-103 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Inventions of Groups I (monomeric monocyclic peptide) and II (dimeric bicyclic peptide) are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the products as claimed differ with respect to their structure and/or chemical properties. Further, Groups I and II are drawn to different subclass. A search of Group I will not encompassed the other. It is a burden to search more than one invention. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 4, 14-17, 25, 52, 56-62 and 89-103 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.
3. Claims 1-3, 12-13, 18, 23-24, 26, 49-51, 53-55, 63 and 72-88 are being acted upon in this Office Action.
4. The following new grounds of rejection are necessitated by the amendment filed 1/2/03 and 1/10/03.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 1-3, 12-13, 18, 23-24, 26, 49-51, 53-55, 63 and 72-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a monomeric monocyclic peptide selected from the group consisting of SEQ ID NO: 5, 6 and 7 which interferes with cell survival of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of

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VEGF receptor-2 and VEGF receptor-3, (2) a monomeric monocyclic peptide selected from the group consisting of SEQ ID NO: 5, 6 and 7 which interferes with cell survival of at least one factor selected from the group consisting of VEGF mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, (3) a monomeric monocyclic peptide selected from the group consisting of SEQ ID NO: 5, 6 and 7 which interferes with cell survival of at least one factor selected from the group consisting of VEGF mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, (4) a monomeric, monocyclic peptide selected from the group consisting of SEQ ID NOS: 5, 6 and 7 produced by a method comprising obtaining a peptide loop fragment from an exposed loop of a growth factor protein or a corresponding loop fragment with one or more amino acid substitutions; measuring beta-beta carbon separation distances on opposing antiparallel strands of the loop fragment; selecting a beta-beta carbon location with a separation distance less than 6 angstroms; providing a cysteine residue in each opposing antiparallel strand at the selected beta-beta location and cyclizing the peptide by oxidizing the provided cysteine residues to form a disulfide bridge between strands, (5) a monomeric monocyclic peptide selected from the group consisting of SEQ ID NOS: 5, 6 and 7 which interferes with cell survival of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3 for inhibition of VEGF, VEGF-C, and VEGF-D mediated cell survival *in vitro*, **does not** reasonably provide enablement for (1) *any* monomeric monocyclic peptide as set forth in claims 1-3, 12-13, 18, 23-24, 26, 49-55, 63 and 72-88 for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

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The specification discloses only various monomeric monocyclic peptides such as the ones shown in Table 1 on page 32 and Table 2 on page 47 of the specification. However, only three monocyclic peptides (peptides number 1-3), which correspond to SEQ ID NO: 5, 6, 7, respectively, have been demonstrated to inhibit VEGF-D Δ N Δ C, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival *in vitro*. Note, none of the monocyclic peptides shown in Table 2 and dimeric bicyclic peptides shown in Table 3 were found to inhibit *any* VEGF, VEGF-D Δ N Δ C, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival *in vitro*. The specification further discloses that heterodimeric bicyclic peptide number 5, which corresponds to SEQ ID NO: 8 linked to SEQ ID NO: 9 (Table 1 on page 32) caused a significant reduction in cell number (Fig 11b). In contrast, neither homodimeric bicyclic peptides 4 and 6, which correspond to SEQ ID NO: 8 linked to SEQ ID NO: 8 or SEQ ID NO: 9 linked to SEQ ID NO: 9 caused a significant change in cell number (page 39). None of the dimeric bicyclic peptides mentioned above appear to be more effective inhibitors than the monomeric monocyclic peptides in VEGF-D induced VEGFR-3 cell survival. The specification also discloses that deletion mutant selected from the group consisting of SEQ ID NO: 10, 11 and 12 having one or two internal amino acid deletion or amino acid substitution fail to inhibit the VEGF-D Δ N Δ C, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival *in vitro*.

Other than the specific monomeric monocyclic peptides mentioned above for inhibiting the VEGF mediated cell survival *in vitro*, the specification does not teach how to make and use *any* monomeric monocyclic peptide because monomeric monocyclic peptide without the amino acid sequence (SEQ ID NO) has no structure. Further, there is insufficient guidance as to the structure, much less function of any monomeric monocyclic peptide "comprises" any core sequence which "is" any receptor binding loop 1 or 2 or 3 of any VEGF such as VEGF, VEGF-C, or VEGF-D because the term "comprises" and "is" open-ended. It expands the to monomeric monocyclic peptide to include additional amino acids at either or both ends, let alone it mimics a native conformation in any receptor binding loop 1 or 2 or 3 of any VEGF such as VEGF, VEGF-C for interfering any biological activity such as inhibition of angiogenesis and/or lymphangiogenesis. Not only any monomeric peptide comprises undisclosed amino acid sequence, there is insufficient guidance as to which amino acid within the loops mentioned above comprising extra undisclosed amino acid residues to be substitute, delete and/or add and whether the resulting monomeric monocyclic peptide would maintain the same structure, would mimic the

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native conformation in the corresponding loops 1, 2, or 3 of any VEGF, much less interfering any biological activity such as inhibition of angiogenesis and/or lymphangiogenesis. Given the indefinite number of undisclosed monomeric monocyclic peptide, there is inadequately working example in the specification demonstrating any undisclosed monomeric monocyclic peptide would interfere with any biological activity of any VEGF such as VEGF-C or VEGF-D mediated by VEGF-receptor-2 and/or VEGF-receptor-3.

Without the specific amino acid residues or SEQ ID NO, there is no structure associated with the phrase "monomeric monocyclic peptide". Since the amino acid sequence of a monomeric monocyclic peptide determines its structural and functional properties, predictability of which changes can be tolerated in a monomeric monocyclic peptide's amino acid sequence and still retain similar functionality (e.g. inhibits angiogenesis) requires a knowledge of and guidance with regard to which amino acids in the monomeric monocyclic peptide's sequence, if any, are tolerant of modification and which are conserved, and detailed knowledge of the ways in which a monomeric monocyclic peptide's structure relates to its functional usefulness. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would mimic the native conformation that lead to interfering with any biological activity of any VEGF such as inhibition of angiogenesis and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.), it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of other functional derivatives of monomeric monocyclic peptide. Without sufficient guidance and working example, the changes which can be made in the structure of undisclosed "monomeric peptide" and still bind and interfere with angiogenesis mediated by VEGF-receptor-2 and VEGF-receptor-3 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue.

Attwood *et al*, of record, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Skolnick *et al*

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teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not necessarily tell one its function (See entire document, Abstract in particular).

As shown in Table 2 of the specification, not all monomeric monocyclic peptides are created equal and demonstrate to have the desired inhibitory activity. Even if the monomeric monocyclic peptides limited to those shown in Table 2, there is no in vivo working example in the specification as filed to support that any monomeric monocyclic peptides mentioned above would inhibit the VEGF mediated cell growth (survival) for treating any disease. A pharmaceutical composition in the absence of in vivo data are unpredictable for the following reasons: (1) the monomeric monocyclic peptide may be inactivated before producing an effect, i.e. such as proteolytic degradation or short half-lives; (2) the monomeric monocyclic peptide may not reach the target area because, i.e. the monomeric monocyclic peptide may not be able to stay long enough in circulation due to clearance or simply has no effect; and (3) other functional properties, known or unknown, may make the monomeric monocyclic peptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Given the undisclosed monomeric monocyclic peptides mentioned above are not enabled, it follows that any monomeric monocyclic peptide which interferes with any biological activity of VEGF-C or VEGF-D mediated by VEGF receptor-2 or VEGFR receptor-3 are not enabled. It also follows that any composition comprising said monomeric monocyclic peptides are not enabled. It also follows that any monomeric monocyclic peptide wherein the constraint maintains a beta-beta carbon separation distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom is not enabled because the term "comprises" is open-ended. There is insufficient guidance as how to maintain distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom having additional undisclosed amino acids residues. With regard to claim 73, term "comprises" is open-ended. It expands the linking group to include additional carbon atoms at either or both ends to infinity, let alone the linking group having extra undisclosed heteroatoms, straight chain, branched and containing one or more of any saturated, unsaturated or aromatic ring. Since any undisclosed monomeric monocyclic peptide mentioned above are not enabled, it follows that any monomeric monocyclic peptide wherein the hetero atom such as the ones recited in claim 74, any constraint such as the ones recited in claims 75-82, 84 and 88 are not enabled. It also follows any residues contributing to

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any said chains of any undisclosed monomeric monocyclic peptide mentioned above such as the ones recited in claims 83 and 85 are not enabled.

With regard to a cyclic peptide "comprising" a peptide sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13 and SEQ ID NO: 14, the term "comprising" is open-ended. It expands the claimed cyclic peptide to include additional amino acid residues at either or both ends. There is insufficient guidance and working examples that after addition of undisclosed amino acid, the resulting cyclic peptide would maintain both structure and function as the claimed cyclic peptide consisting of the SEQ ID NOS mentioned above. Given the indefinite number of undisclosed amino acids that can be added to said cyclic peptide, it is unpredictable which undisclosed cyclic peptide would be useful for inhibiting the VEGF induced VEGFR-2 and VEGFR-3 mediated cell survival even in vitro.

With regard to claim 18, there is insufficient guidance and working that *any* cyclic peptide produced by the method of Claim 10 would interfere with *any* activity of at least one factor such as VEGF, VEGF-C, VEGF-D mediated at least one receptor such as VEGFR-2 and VEGFR-3. The specification discloses that deletion mutant selected from the group consisting of SEQ ID NO: 10, 11 and 12 having one or two internal amino acid deletion or amino acid substitution **fail to inhibit** the VEGF- Δ N Δ C, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and/or VEGFR-3 mediated cell survival in vitro. The claim as written is inconsistent with the data provided in the specification.

For these reasons, it would require undue experimentation for one even skilled in the art to practice the claimed invention. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In *re wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/2/03 and 1/10/03 have been fully considered but are not found persuasive.

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Applicants' position is that (1) it is routine experimentation to arrive at the claimed monocyclic peptides and to test whether they have the requisite biological activity. (2) rather than all of the claimed peptides, the working examples are based on the loop fragments of the growth factors VEGF, VEGF-C, or VEGF-D. Because the loops are known to have a small number of residues, only a very limited amount of screening would be required to identify those that when cyclized, maintain its affinity with one of VEGFs. (3) no undue experimentation is required and no in vivo data is required for the claimed invention.

In response to Applicant's arguments, the term "comprises" and "is" open-ended. It expands the to monomeric monocyclic peptide to include additional amino acids at either or both ends, let alone it mimics a native conformation in any receptor binding loop 1 or 2 or 3 of any VEGF such as VEGF, VEGF-C for interfering any biological activity such as inhibition of angiogenesis and/or lymphangiogenesis. The specification does not teach how to make and use *any* monomeric monocyclic peptide because monomeric monocyclic peptide without the amino acid sequence (SEQ ID NO) has no structure. Further, there is insufficient guidance as to the structure, much less function of any monomeric monocyclic peptide "comprises" any core sequence which "is" any receptor binding loop 1 or 2 or 3 of any VEGF such as VEGF, VEGF-C, or VEGF-D because the term "comprises" and "is" open-ended. It expands the to monomeric monocyclic peptide to include additional amino acids at either or both ends, let alone it mimics a native conformation in any receptor binding loop 1 or 2 or 3 of any VEGF such as VEGF, VEGF-C for interfering any biological activity such as inhibition of angiogenesis and/or lymphangiogenesis. Not only any monomeric peptide comprises undisclosed amino acid sequence, there is insufficient guidance as to which amino acid within the loops mentioned above comprising extra undisclosed amino acid residues to be substitute, delete and/or add and whether the resulting monomeric monocyclic peptide would maintain the same structure, would mimic the native conformation in the corresponding loops 1, 2, or 3 of any VEGF, much less interfering any biological activity such as inhibition of angiogenesis and/or lymphangiogenesis. Given the indefinite number of undisclosed monomeric monocyclic peptide, there is inadequately working example in the specification demonstrating that any undisclosed monomeric monocyclic peptide would interfere with any biological activity of any VEGF such as VEGF-C or VEGF-D mediated by VEGF-receptor-2 and/or VEGF-receptor-3.

Without the specific amino acid residues or SEQ ID NO, there is no structure associated with the phrase "monomeric monocyclic peptide". Since the amino acid sequence of a

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monomeric monocyclic peptide determines its structural and functional properties, predictability of which changes can be tolerated in a monomeric monocyclic peptide's amino acid sequence and still retain similar functionality (e.g. inhibits angiogenesis) requires a knowledge of and guidance with regard to which amino acids in the monomeric monocyclic peptide's sequence, if any, are tolerant of modification and which are conserved, and detailed knowledge of the ways in which a monomeric monocyclic peptide's structure relates to its functional usefulness. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would mimic the native conformation and lead to interfering with any biological activity of any VEGF such as inhibition of angiogenesis and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.), it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of other functional derivatives of monomeric monocyclic peptide. Without sufficient guidance and working example, the changes which can be made in the structure of "monomeric peptide" and still bind and interfere with angiogenesis mediated by VEGF-receptor-2 and VEGF-receptor-3 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue.

7. Claims 1-3, 12-13, 18, 23-24, 26, 49-51, 53-55, 63 and 72-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* monomeric monocyclic peptide as set forth in claims 1-3, 12-13, 18, 23-24, 26, 49-55, 63 and 72-88 for treating *any* disease.

The specification discloses only various monomeric monocyclic peptides such as the ones shown in Table 1 on page 32 and Table 2 on page 47 of the specification. However, only three monocyclic peptides (peptides number 1-3), which correspond to SEQ ID NO: 5, 6, 7, respectively, have been demonstrated to inhibit VEGF-D Δ N Δ C, VEGF-C, VEGF-D and mouse

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VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro. Note, none of the monocyclic peptides shown in Table 2 and dimeric bicyclic peptides shown in Table 3 were found to inhibit any VEGF, VEGF-D Δ N Δ C, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro. The specification further discloses that heterodimeric bicyclic peptide number 5, which corresponds to SEQ ID NO: 8 linked to SEQ ID NO: 9 (Table 1 on page 32) caused a significant reduction in number (Fig 11b). In contrast, neither homodimeric bicyclic peptides 4 and 6, which correspond to SEQ ID NO: 8 linked to SEQ ID NO: 8 or SEQ ID NO: 9 linked to SEQ ID NO: 9 caused a significant change in cell number (page 39). None of the dimeric bicyclic peptides mentioned above appear to be more effective inhibitors than the monomeric monocyclic peptides in VEGF-D induced VEGFR-3 cell survival. The specification also discloses that deletion mutant selected from the group consisting of SEQ ID NO: 10, 11 and 12 having one or two internal amino acid deletion or amino acid substitution fail to inhibit the VEGF-D Δ N Δ C, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro.

With the exception of the specific monomeric monocyclic peptides mentioned above, there is insufficient written description about the structure associated with function of *any* "monomeric monocyclic peptide" mentioned above because the term "comprises" and "is" open-ended. It expands the to monomeric monocyclic peptide to include additional amino acids at either or both ends, let alone it mimics a native conformation in any receptor binding loop 1 or 2 or 3 of any VEGF such as VEGF, VEGF-C for interfering any biological activity such as inhibition of angiogenesis and/or lymphangiogenesis. Further, the term "monomeric monocyclic peptide" without the amino acid sequence (SEQ ID NO) has no structure, much less about its function. Further, there is inadequate written description about the structure associated with function of any undisclosed monomeric monocyclic peptide "comprises" any core sequence which "is" any receptor binding loop 1 or 2 or 3 of any VEGF such as VEGF, VEGF-C, or VEGF-D because the terms "comprises" and "is" are open-ended. It expands the to monomeric monocyclic peptide to include additional amino acids at either or both ends, let alone it mimics a native conformation in any receptor binding loop 1 or 2 or 3 of any VEGF such as VEGF, VEGF-C for interfering any biological activity such as inhibition of angiogenesis and/or lymphangiogenesis. Given the indefinite number of undisclosed monomeric peptide, it follows that which amino acid within the loops mentioned above comprising extra undisclosed amino acid residues to be substitute, delete and/or add is not adequately described. It also follows that

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any composition comprising any undisclosed monomeric monocyclic peptides are not adequately described. It also follows that any monomeric monocyclic peptide wherein the constraint maintains a beta-beta carbon separation distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom is not adequately described because the term "comprises" is open-ended. There is insufficient written description as how to maintain distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom having additional undisclosed amino acids residues. With regard to claim 73, the term "comprises" is open-ended. It expands the linking group to include additional carbon atoms at either or both ends to infinity, let alone the linking group having extra undisclosed heteroatoms, straight chain, or branched and containing one or more of any saturated, unsaturated or aromatic ring. Since any undisclosed monomeric monocyclic peptide mentioned above are not adequately described, it follows that any monomeric monocyclic peptide wherein the hetero atom such as the ones recited in claim 74, any constraint such as the ones recited in claims 75-82, 84 and 88 are not adequately described. It also follows any residues contributing to any said chains of any undisclosed monomeric monocyclic peptide mentioned above such as the ones recited in claims 83 and 85 are not adequately described.

The specification discloses only various monomeric monocyclic peptides such as the ones shown in Table 1 on page 32 and Table 2 on page 47 of the specification. However, only three monocyclic peptides (peptides number 1-3), which correspond to SEQ ID NO: 5, 6, 7, respectively, have been demonstrated to inhibit VEGF-D Δ N Δ C, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro. Given that there are only three monomeric monocyclic peptides selected from the group consisting of SEQ ID NO: 5, 6 and 7 have been demonstrated to be effective as inhibitors for VEGF induced VEGFR-2 and VEGFR-3 mediated cell survival, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species functional monomeric monocyclic peptide to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/2/03 and 1/10/03 have been fully considered but are not found persuasive.

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Applicants' position is that (1) the specification describes how variants of the specifically disclosed core sequences can be obtained by an ordinary skill persons, and guidelines as to which specific amino acid residue of the polypeptide are conserved for maintaining a receptor binding activity. (2) the claimed genus is not highly variable in view of the fact that the loop sequences are relatively short, well-characterized and have highly conserved structural and functional characteristics.

In response to Applicant's arguments, the claims are not drawn to the specifically disclosed core sequences. Further, the terms "comprises" and "is" are open-ended. It expands the to monomeric monocyclic peptide to include additional amino acids at either or both ends, let alone it mimics a native conformation in any receptor binding loop 1 or 2 or 3 of any VEGF such as VEGF, VEGF-C for interfering any biological activity such as inhibition of angiogenesis and/or lymphangiogenesis. Further, the specification as filed does not disclose the specific amino acid sequence for each receptor binding loop such as loops 1, 2, 3 of any VEGF and one even skill in the art cannot appraise the metes and bounds of the enabling disclosure of said loop 1, 2 or 3 of any VEGF, let alone having various amino acid substitution, or deletion. Given the indefinite number of undisclosed monomeric peptide, it follows that which amino acid within the undisclosed loops mentioned above comprising extra undisclosed amino acid residues to be substitute, delete and/or add is not adequately described. It also follows that any composition comprising any undisclosed monomeric monocyclic peptides are not adequately described. It also follows that any monomeric monocyclic peptide wherein the constraint maintains a beta-beta carbon separation distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom is not adequately described because the term "comprises" is open-ended. There is insufficient written description as how to maintain distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom having additional undisclosed amino acids residues. With regard to claim 73, the term "comprises" is open-ended. It expands the linking group to include additional carbon atoms at either or both ends to infinity, let alone the linking group having extra undisclosed heteroatoms, straight chain, branched and containing one or more of any saturated, unsaturated or aromatic ring. Since any undisclosed monomeric monocyclic peptide mentioned above are not adequately described, it follows that any monomeric monocyclic peptide wherein the hetero atom such as the ones recited in claim 74, any constraint such as the ones recited in claims 75-82, 84 and 88 are not adequately described. It also follows any residues contributing to any side chains from any loops mentioned

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above of any undisclosed monomeric monocyclic peptide mentioned above such as the ones recited in claims 83 and 85 are not adequately described.

8. Claims 1-3, 12-13, 18, 23-24, 26, 63 and 72-88 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "a receptor-binding loop 1, 2 or 3 of VEGF, VEGF-C" in Claims 1, 12 and dependent claims thereof represents a departure from the specification and the claims as originally filed because "a receptor-binding loop 1, 2 or 3 of VEGF, VEGF-C" has no support in the claims and the specification as originally filed. The specification discloses a monomeric monocyclic peptide inhibitor based on loop 1, 2 or 3 of **VEGF-D** (See on page 13 at line 27). Further, Applicants have not pointed out the support for said phrase.

Further, the "first linking group at one end of the core sequence and a second linking group at the other end of the core sequence wherein the first and second linking groups are connected to form a constraint that cyclizes the peptide such that receptor-binding loop 1, 2 or 3 or the corresponding loop fragment mimics a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D" in claims 1 and dependent claims thereof represents a departure from the specification and the claims as originally filed because said phrase has no support in the specification and the claims as originally filed. Further, Applicants have not pointed out the support for said phrase.

The "further comprises deleting at least one amino acid from said loop fragment prior to cyclizing the peptide" in claim 18 has no support in the specification or the claims as originally filed. Applicants have not pointed out the support for said phrase.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

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10. Claims 76-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "C-terminal carboxyl acid **function**" in claim 76 is ambiguous and indefinite because one of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

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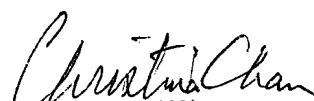
14. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

March 10, 2003


CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600